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# U.S. prescribing trends of fentanyl, opioids, and other pain medications in outpatient and emergency department visits from 2006 to 2015

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ABSTRACT

The United States is currently facing an epidemic of opioid-related deaths, increasingly associated with fentanyl use. Our objective was to characterize rates of fentanyl, general opioid and non-opioid pain medication prescription at a national level in both outpatient and emergency department settings. We used a retrospective cross-sectional research design using data from the 2006–2015 National Ambulatory Medical Care Surveys and National Hospital Ambulatory Medical Care Surveys. Between 2006–2015, 66,987 (17.4%) of 390,538 office-based outpatient visits (nationally-representative of 961 million visits) and 134,953 (45.0%) of 305,570 ED visits (nationally-representative of 130 million visits) listed a pain medication prescription. The proportion of all outpatient visits in which any pain medication was prescribed increased from 15.0% in 2006–2007 to 20.5% in 2014–2015 ($p < 0.001$). The proportion of all outpatient visits in which any fentanyl product was prescribed remained stable at 0.3% and 0.4% ($p = 0.32$), but increased among ED visits from 0.5% to 1.1% ($p = 0.006$). In contrast, the proportion of all outpatient visits in which any opioid product was prescribed increased from 6.6% to 9.7% ($p < 0.001$), but remained relatively stable among ED visits from 26.2% to 24.4% ($p = 0.07$). Non-opioid pain medication prescription increased in both settings, from 9.7% to 13.7% ($p < 0.001$) in the outpatient setting and from 25.6% to 27.6% ($p = 0.02$) in the ED setting between 2006–2007 and 2014–2015, respectively. To address current opioid crisis, both clinical and public health interventions are needed, such as targeted education outreach on evidence-based opioid prescribing and non-opioid alternatives.

## 1. Introduction

The United States is currently facing an opioid epidemic, which began in the mid-1990s with increased pharmaceutical marketing, as well as promotion by both hospital accrediting bodies and official medical societies (Kolodny et al., 2015). Emergency department (ED) visits for opioid overdoses rose 30% across the country from July 2016 through September 2017 (Centers for Disease Control and Prevention, 2017, 2018). Opioid-related deaths were five times higher in 2016 than 1999 (Centers for Disease Control and Prevention, 2017). In response, the Centers for Disease Control and Prevention (CDC) issued guidelines in 2013 encouraging the replacement of opioid medications with non-opioid alternatives to treat chronic pain (Dowell et al., 2016). Despite such efforts, fentanyl prescribing and its related harms have been rising nationwide. Fentanyl, a schedule II opioid, is approximately 100 times more potent than morphine, acts rapidly, and has a high potential for addiction (Jumbelic, 2010; Roxburgh et al., 2013). Deaths from fentanyl (both prescription and illicit) and other non-methadone synthetic opioids (with the exception of methadone) climbed from 8% in 2010 to 18% in 2015 (Hedegaard et al., 2017). Another study reported that the number of illicit fentanyl-related deaths increased from 2128 in 2014 to 15,646 in 2016, indicating a surge of illicit fentanyl use (Lilly, 2018).

### 1.1. Importance

While a study of nationwide opioid prescriptions from 2002 to 2013 suggested that opioid prescriptions began to decline prior to the 2013 CDC guideline announcement (Dart et al., 2015a, 2015b), the response to these guidelines has not been very well studied. Furthermore, while the substantial recent increase in fentanyl-associated deaths suggests an

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increasing rate of fentanyl distribution (Seth et al., 2018; Whalen, 2017), it remains unknown whether the source of this increased availability is from clinician prescriptions or from illicit distribution (e.g., black markets). A recent set of CDC reports show that in states with the highest burden of fentanyl-related deaths, the increase in deaths has no correlation with changes in fentanyl prescription (Gladden, 2016; O'Donnell et al., 2017); instead, they are likely an effect of illicit fentanyl distribution (Lilly, 2018). However, these technical reports are limited as they investigated fentanyl prescribing at the state level only, and did not differentiate between different prescriber settings (e.g., outpatient care versus emergency department). Examining these two different prescriber settings is important as the acuity of care is very different, which impacts the appropriateness of pain medication prescribing (e.g., opioid therapy may be indicated for acute pain and not for most causes of chronic pain).

### 1.2. Goals of this investigation

Our objective was to investigate and compare current prescribing rates of opioid medications, including fentanyl, and of non-opioid medications in the outpatient and emergency department settings using a nationally-representative sample.

## 2. Methods

### 2.1. Study design and setting and selection of participants

We used 2006–2015 data from the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS), which provide nationally representative samples of office-based outpatient visits and emergency department visits, respectively (National Center for Health Statistics, 2017b). NAMCS and NHAMCS both sample non-federally employed physicians who are primarily engaged in direct patient care. The data provide an analytic base that serves as an important tracking tool on ambulatory and emergency care utilization regarding national trends, medication use, and practice patterns in the US (National Center for Health Statistics, 2017a). Both NAMCS and NHAMCS utilize a complex survey design and sampling weights (i.e., unequal probability of selection, clustering, and stratification), where physicians are selected in the first stage and visits in the second stage. Samples included 390,538 visits in NAMCS and 305,570 visits in NHAMCS. Additional information regarding descriptions, questionnaires, sampling methodology and datasets is publicly available on the NAMCS and NHAMCS website (https://www.cdc.gov/nchs/ahcd/about_ahcd.htm).

### 2.2. Measures

#### 2.2.1. Pain medications

To characterize pain medication prescribing, we examined the first eight medications listed for all outpatient and ED visits, ensuring consistency across all survey years. We constructed three indicator variables using generic names of medications: fentanyl and its analogue products (i.e., fentanyl droperidol-fentanyl, alfentanil, sufentanil, and remifentanil), all opioid products other than fentanyl (including their analogues), and all other non-opioid pain medications. Opioid products other than fentanyl consisted of the following medications: codeine, meperidine, methadone, alfentanil, hydromorphone, morphine, oxycodone, pentazocine, propoxyphene, sufentanil, opium, levorphanol, oxymorphone, butorphanol, nalbuphine, buprenorphine, hydrocodone, dihydrocodeine, remifentanil, tapentadol, tramadol, and their combined products. Other non-opioid pain medications are nonsteroidal anti-inflammatory drugs (NSAIDs), non-analgesics, and other drugs (i.e., acetaminophen, aspirin, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, phenylbutazone, piroxicam, tolmetin, gabapentin, and pregabalin).

#### 2.2.2. Demographic and clinical covariates

We included a number of patient demographic and clinical covariates provided during visits. Demographic variables included: age ($<19$, 19–44, 45–64, or $\geq 65$), gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), primary source of payment (private, Medicare, Medicaid, or other). Medicare is a federal program that provides health insurance coverage for US adults aged 65 or older, and Medicaid is a state and federal program that provides health insurance coverage for low-income individuals and families (U.S. Department of Health and Human Services, 2015). Clinical variables included visit diagnosis and physician specialty. Both NAMCS and NHAMCS collect up to three visit diagnoses for each sampled visit using the *International Classification of Diseases, 9th edition, Clinical Modification* (ICD-9-CM) diagnostic codes. We categorized visit diagnosis into three groups: cancer-related pain diagnoses (i.e., 140–239 or 338.3X), non-cancer related pain diagnoses (i.e., 338.XX, 350.1X-350.2X, 354.4X, 355.71, 379.91. 388.7X, 719.4X, 724.1X-724.2X, 729.1X, 780.96, 786.5X, or 789.XX), and no pain-related diagnosis. For physician specialty, we distinguished between generalists (i.e., general/family practice, internal medicine, pediatrics, and obstetrics and gynecology) vs. other in NAMCS. In NHAMCS, we distinguished clinical specialty by clinical degree (i.e., MD vs. other). We also reported number of visits in the past 12 months (0, 1–2, 3–5, or $\geq 6$), number of chronic conditions (0–1 or $\geq 2$), and number of concomitant medications (0–5 or $\geq 6$) prescribed in NAMCS datasets.

### 2.3. Ethics and data availability

As we used publicly available de-identified data, our study was deemed the Institutional Review Board exempt by Yale School of Medicine (#2000021850). The datasets generated and/or analysed during the current study are available in the NAMCS/NHAMCS repository (https://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm).

### 2.4. Statistical analysis

We determined the proportion of visits for which any pain medication was prescribed and examined associations with selected characteristics (e.g., age, sex, race/ethnicity, clinical comorbidities, concomitant medication use, and physician specialty), using Bonferroni-adjusted bivariate analyses. Next, we determined the proportion of visits for which any pain medication was prescribed across survey years, overall and for each pain medication class, also stratifying overall analyses by selected patient and visit characteristics. We used Chi-Square analysis to compare rates in 2006–2007 and 2014–2015. All analyses were conducted using Stata MP/6-Core version 15.1 (College Station, TX), accounting for the complex survey design and sampling weights.

## 3. Results

### 3.1. Selected characteristics of the study subjects

Between 2006 and 2015, 66,987 (17.4%) of 390,538 office-based outpatient visits (nationally-representative of 961 million visits) and 134,953 (45.0%) of 305,570 ED visits (nationally-representative of 130 million visits) listed a pain medication prescription (Table 1). 56.3% of office-based outpatient visits were to primary care physicians, and of these visits, 18.3% involved a prescription for a pain medication. Among office-based outpatient visits, pain medication prescription was highest among patients aged 45–64, non-Hispanic Black patients, patients with Medicare coverage, patients receiving care from primary care physicians, and patients receiving care for a pain-related diagnosis (all $p$-values $< 0.001$). Furthermore, visits involved with two or more chronic conditions and six or more medications concomitantly prescribed were also associated with receiving pain medications (all $p$-

**Table 1**
Selected characteristics (weighted %) of visits in which pain medications were prescribed, 2006–2015 NAMCS and NHAMCS.

| | NAMCS | | | NHAMCS | | |
|---|---|---|---|---|---|---|
| | Total (column %) | Pain medication prescription (row %) | *p*-Value† | Total (column %) | Pain medication prescription (row %) | *p*-Value† |
| Sample size | | | | | | |
| Unweighted sample | 390,538 | 66,987 | | 305,570 | 134,953 | |
| Weighted visits | 961,261,367 | 167,349,606 | | 130,155,321 | 58,568,338 | |
| Age | | | | | | |
| < 19 | 18.9 | 9.6 | < 0.001 | 24.1 | 40.0 | < 0.001 |
| 19–44 | 24.1 | 17.3 | | 39.0 | 51.9 | |
| 45–64 | 29.7 | 21.8 | | 21.7 | 47.8 | |
| ≥65 | 27.3 | 18.1 | | 15.2 | 31.1 | |
| Gender | | | | | | |
| Female | 58.5 | 17.6 | 0.045 | 54.9 | 43.6 | < 0.001 |
| Male | 41.5 | 17.1 | | 45.1 | 46.1 | |
| Race/ethnicity | | | | | | |
| Non-Hispanic White | 71.8 | 17.5 | < 0.001 | 59.7 | 44.9 | 0.001 |
| Non-Hispanic Black | 10.3 | 19.0 | | 22.5 | 44.8 | |
| Hispanic | 12.5 | 16.9 | | 14.6 | 46.3 | |
| Other[a)] | 5.3 | 14.1 | | 3.2 | 43.3 | |
| Primary source of payment | | | | | | |
| Private | 53.7 | 15.3 | < 0.001 | 32.6 | 47.8 | < 0.001 |
| Medicare | 25.9 | 20.1 | | 18.7 | 35.5 | |
| Medicaid | 12.5 | 17.7 | | 28.8 | 45.3 | |
| Other | 7.9 | 21.6 | | 19.9 | 50.0 | |
| Physician specialty | | | | | | |
| Generalists[b)] | 56.3 | 18.3 | < 0.001 | – | – | – |
| Other[c)] | 43.7 | 16.3 | | – | – | |
| Clinician specialty | | | | | | |
| MDs | – | – | – | 90.1 | 45.8 | < 0.001 |
| Other[d)] | – | – | | 9.9 | 39.6 | |
| Repeat of visits in the past 12 months | | | | | | |
| 0 visit | 6.9 | 12.4 | < 0.001 | – | – | – |
| 1–2 visits | 36.4 | 15.7 | | – | – | |
| 3–5 visits | 31.2 | 18.3 | | – | – | |
| 6+ visits | 25.4 | 21.2 | | – | – | |
| Chronic conditions[e)] | | | | – | – | – |
| < 2 | 68.2 | 14.7 | < 0.001 | | | |
| ≥2 | 31.8 | 23.8 | | | | |
| Concomitant medications prescribed | | | | – | – | – |
| < 6 | 83.9 | 13.0 | < 0.001 | | | |
| ≥6 | 16.1 | 37.7 | | | | |
| Visit diagnosis | | | | | | |
| Cancer-related[f)] | 4.7 | 14.9 | < 0.001 | 0.6 | 46.5 | < 0.001 |
| Other pain-related[g)] | 5.0 | 43.8 | | 13.0 | 60.6 | |
| No indication | 90.3 | 16.1 | | 86.5 | 42.7 | |

Note: † compares proportion differences by any pain prescription using a weight-corrected, Bonferroni-adjusted chi-squared statistic. a) includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups; b) includes general/family practice, internal medicine, pediatrics, and obstetrics and gynecology; c) includes psychiatry, general surgery, orthopedic surgery, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; d) includes physician assistants (PAs) and nurse practitioners (NPs); e) was based 14 chronic conditions (yes/no) collected by the NAMCS (e.g., arthritis, congestive heart failure, and diabetes); f) was based on ICD-9-CM diagnostic codes 140–239, 338.3X; and g) was based on ICD-9-CM codes 338.XX, 350.1X-350.2X, 354.4X, 355.71, 379.91. 388.7X, 719.4X, 724.1X-724.2X, 729.1X, 780.96, 786.5X, 789.XX.

values < 0.001). Among ED visits, pain medication prescription was highest among patients aged 19–44, males, Hispanic patients, patients with private insurance, patients receiving care from MDs, and patients receiving care for a pain-related diagnosis (all *p*-values < 0.001).

### 3.2. National prescribing trends of opioids, fentanyl and other pain medications

The proportion of all outpatient visits in which any pain medication was prescribed increased significantly from 15.0% in 2006–2007 to 20.5% in 2014–2015 ($p < 0.001$). Among ED visits, the proportion did not change significantly, ranging from 44.2% in 2006–2007 to 44.5% in 2014–2015 ($p = 0.72$) (Table 2).

The proportion of all outpatient visits in which any fentanyl products was prescribed remained stable at 0.3% in 2006–2007 and 0.4% in 2014–2015 ($p = 0.32$), but prescribing of fentanyl product increased significantly among ED visits from 0.5% in 2006–2007 to 1.1% in 2014–2015 ($p = 0.006$). In contrast, the proportion of all outpatient visits in which any non-fentanyl opioid product was prescribed increased significantly from 6.6% in 2006–2007 to 9.7% in 2014–2015 ($p < 0.001$), but remained relatively stable among ED visits from 26.2% in 2006–2007 to 24.4% in 2014–2015 ($p = 0.07$). Non-opioid pain medication prescription increased in both settings, from 9.7% to 13.7% ($p < 0.001$) in the outpatient setting and from 25.6% to 27.6% ($p = 0.02$) in the ED setting in 2006–2007 and 2014–2015, respectively.

**Table 2**
Pain medication prescribing trends, 2006–2015 NAMCS and NHAMCS.

| | Years (%) | | | | | 2006–2007 vs. 2014–2015, *p*-Value[α] |
|---|---|---|---|---|---|---|
| | 2006–2007 | 2008–2009 | 2010–2011 | 2012–2013 | 2014–2015 | |
| NAMCS | | | | | | |
| Visits in which any pain medication prescribed | 15.0% | 16.4% | 17.4% | 18.0% | 20.5% | < 0.001 |
| Visits in which any pain medication from the specific class prescribed | | | | | | |
| Fentanyl and analogues* | 0.3% | 0.3% | 0.2% | 0.3% | 0.4% | 0.318 |
| Opioid and combined products† | 6.6% | 7.7% | 8.1% | 9.0% | 9.7% | < 0.001 |
| Non-analgesics, NSAIDs, tylenol, and non-opioid combined products‡ | 9.7% | 10.5% | 11.2% | 11.8% | 13.7% | < 0.001 |
| NHAMCS | | | | | | |
| Visits in which any pain medication prescribed | 44.2% | 45.6% | 46.8% | 44.0% | 44.5% | 0.719 |
| Visits in which any pain medication from the specific class prescribed | | | | | | |
| Fentanyl and analogues* | 0.5% | 0.5% | 0.9% | 0.7% | 1.1% | 0.006 |
| Opioid and combined products† | 26.2% | 27.0% | 28.7% | 26.0% | 24.4% | 0.072 |
| Non-analgesics, NSAIDs, tylenol, and non-opioid combined products‡ | 25.6% | 26.6% | 26.8% | 25.7% | 27.6% | 0.016 |

Note: α compares proportion (%) differences between 2006 and 2007 and 2014–2015, using a weight-corrected, Bonferroni-adjusted chi-squared statistic. *includes fentanyl and droperidol-fentanyl, alfentanil, sufentanil, and remifentanil; †codeine, meperidine, methadone, hydromorphone, morphine, oxycodone, pentazocine, propoxyphene, opium, levorphanol, oxymorphone, butorphanol, nalbuphine, buprenorphine, hydrocodone, dihydrocodeine, tapentadol, tramadol, and their combined products; ‡includes gabapentin and pregabalin for non-analgesics, and NSAIDs include acetaminophen, aspirin, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac,naproxen, phenylbutazone, piroxicam, and tolmetin.

### 3.3. Factors of prescribing any pain medication

There were several patient factors predictive of higher rates of prescribing of any pain medication among both outpatient and ED visits (Table 3). Among outpatient visits, pain medication prescription was highest among visits by patients aged 45–64 years, increasing significantly over time to 25.6% in 2014–2015 ($p < 0.001$), and among visits by patients with Medicare, increasing significantly over time to 24.2% in 2014–2015 ($p < 0.001$). In contrast, among ED visits, pain medication prescription was lowest among visits by patients with Medicare insurance, but increased significantly over time to 36.4% in 2014–2015 ($p = 0.003$).

## 4. Discussion

In this study of pain medication prescribing in a nationally-representative sample of outpatient and ED visits from 2006 to 2015, overall rates of pain medication prescribing were high, with a prescription provided among approximately one in five outpatient visits and nearly one in two ED visits. Over this period, we found increased opioid pain medication prescribing in the outpatient setting, rising to nearly one in twelve visits, and a small but significant increase in fentanyl prescribing in the ED, peaking at a rate of prescribing of 1.1% of all ED visits in 2014–2015. Finally, reassuringly, there was an increase in non-opioid pain medication prescribing in both the outpatient and ED settings, which has not been previously reported or well-investigated.

The prescription of opioid medications increased in the outpatient setting. Chronic non-cancer-related pain is a common presentation in primary care, and the difficulties of determining when to prescribe opioids, and for how long, has been acknowledged in multiple studies (Harle et al., 2015; Jamison et al., 2014). Our results suggest the need to implement several interventions in order to reduce opioid prescribing for chronic pain in the primary care setting. For instance, there have been numerous efforts to encourage appropriate opioid prescribing, including targeted physician education (Leece et al., 2017). Requiring patients to have a structured care system comprising of periodic visits dedicated to monitoring and discussion of their current opioid medications has been shown to reduce opioid prescriptions (McCann et al., 2018). Ongoing education for patients who are currently struggling with opioid dependence is especially important. Patients with opioid dependence are more likely to experience an opioid overdose event (Substance Abuse and Mental Health Services Administration, 2018) and a recent study has shown that patients who have experienced a non-fatal overdose are at high risk of fatal opioid overdose throughout this period (Olfson et al., 2018). A multicomponent system involving a nurse care manager, electronic registry, data-driven academic detailing (i.e., face-to-face education of prescribers by trained healthcare professionals in order to improve evidence-based prescribing of targeted drugs), and clinical decision support (such as care reminders, up-to-date guidelines, recommendations, and databases that can provide information relevant to particular patients) have also shown to improve adherence to opioid-prescribing guidelines (Cushman, 2017; Liebschutz et al., 2017).

There was a small but significant increase in fentanyl prescribing which is important to acknowledge. This was particularly notable in the ED setting, where patients often have a short stay and are discharged without monitoring or follow-up care, inherently leading to increased risk of abuse potential (Compton and Volkow, 2006). Strategies for preventing subsequent fentanyl diversion after ED prescription are three-fold: ED providers could dispense a small amount of fentanyl with no or minimal refills; they could then schedule primary care follow-up for further pain management, with instructions that therapy be non-opioid in nature; and/or they could utilize alternative, non-opioid analgesic treatments within the ED setting before patients are discharged.

Conversely, it is promising to see that despite the small increase in fentanyl-specific prescribing, opioid prescribing in the ED decreased from 2010 to 2015, with the most notable decline between 2010 and 2013. These results are consistent with previous studies both at the state-level (O'Donnell et al., 2017; Peterson et al., 2016; Somerville et al., 2017) and nationally (Cicero et al., 2017), suggesting that, regardless of prescriber setting, the recent increase in fentanyl-related deaths is less likely attributable to physician prescribing and more likely represents non-prescription distribution. This may actually be the effect of efforts to reduce opioid prescribing and limit utilization of opioids by pain specialists, which some have raised concerns about having unintended downstream consequences, including opening up a market for illicit opioid distribution (Cicero et al., 2014).

Given that many of the fentanyl-related deaths are likely attributable to illicitly manufactured fentanyl, targeted efforts towards monitoring illicit fentanyl production and distribution are needed in addition to monitoring prescription fentanyl diversion. Multiple strategies can be implemented, such as increased access to rapid-acting potent naloxone for high-risk individuals and their close contacts, adding

**Table 3**
Stratified analysis of pain medication prescribing trends by key patient and visit characteristics, 2006–2015 NAMCS and NHAMCS.

| | Years (%) | | | | | 2006–2007 vs. 2014–2015, *p*-Value[α] |
|---|---|---|---|---|---|---|
| | 2006–2007 | 2008–2009 | 2010–2011 | 2012–2013 | 2014–2015 | |
| NAMCS | | | | | | |
| Visit diagnosis | | | | | | |
| Cancer-related[*] | 11.9% | 14.3% | 16.0% | 15.2% | 16.4% | 0.037 |
| Other pain-related[†] | 43.4% | 43.6% | 43.3% | 44.2% | 44.1% | 0.846 |
| No indication | 13.9% | 15.1% | 16.0% | 16.5% | 19.1% | < 0.001 |
| Physician specialty | | | | | | |
| Generalist[‡] | 16.3% | 17.7% | 17.8% | 18.4% | 21.6% | < 0.001 |
| Other[§] | 13.1% | 14.4% | 16.8% | 17.6% | 19.2% | < 0.001 |
| Age | | | | | | |
| < 19 | 9.4% | 10.1% | 10.1% | 8.4% | 10.0% | 0.504 |
| 19–44 | 15.7% | 15.5% | 17.6% | 18.7% | 19.5% | 0.001 |
| 45–64 | 18.8% | 20.3% | 21.7% | 22.5% | 25.6% | < 0.001 |
| ≥65 | 14.6% | 17.0% | 18.2% | 19.0% | 21.4% | < 0.001 |
| Gender | | | | | | |
| Female | 15.0% | 16.9% | 17.6% | 18.1% | 20.6% | < 0.001 |
| Male | 14.9% | 15.5% | 17.1% | 18.0% | 20.2% | < 0.001 |
| Race/ethnicity | | | | | | |
| Non-Hispanic White | 15.1% | 16.7% | 17.5% | 17.9% | 20.8% | < 0.001 |
| Non-Hispanic Black | 15.6% | 16.7% | 19.8% | 19.6% | 22.9% | < 0.001 |
| Hispanic | 14.5% | 15.1% | 16.6% | 18.9% | 19.5% | 0.003 |
| Other[‖] | 13.4% | 14.1% | 12.7% | 15.0% | 15.3% | 0.331 |
| Primary source of payment | | | | | | |
| Private | 13.5% | 14.8% | 15.2% | 15.7% | 17.8% | < 0.001 |
| Medicare | 15.8% | 19.1% | 19.8% | 20.9% | 24.2% | < 0.001 |
| Medicaid | 16.6% | 15.9% | 19.0% | 17.3% | 19.5% | 0.055 |
| Other | 19.1% | 19.5% | 22.6% | 23.9% | 22.8% | 0.168 |
| NHAMCS | | | | | | |
| Visit diagnosis | | | | | | |
| Cancer-related[*] | 41.0% | 46.2% | 46.8% | 47.8% | 49.3% | 0.074 |
| Other pain-related[†] | 57.9% | 62.2% | 63.2% | 60.0% | 59.3% | 0.262 |
| No indication | 42.5% | 43.3% | 44.3% | 41.3% | 41.9% | 0.548 |
| Clinician specialty | | | | | | |
| MDs | 45.4% | 46.8% | 47.5% | 44.7% | 44.8% | 0.580 |
| Other[¶] | 35.5% | 36.5% | 43.5% | 37.7% | 42.5% | < 0.001 |
| Age | | | | | | |
| < 19 | 39.6% | 41.9% | 41.2% | 39.0% | 38.2% | 0.350 |
| 19–44 | 51.4% | 52.9% | 54.2% | 50.0% | 51.1% | 0.785 |
| 45–64 | 45.5% | 47.5% | 49.9% | 47.4% | 48.6% | 0.024 |
| ≥65 | 30.1% | 30.1% | 31.9% | 31.1% | 32.1% | 0.118 |
| Gender | | | | | | |
| Female | 45.2% | 46.7% | 48.0% | 44.9% | 45.8% | 0.570 |
| Male | 42.9% | 44.2% | 45.4% | 42.6% | 42.9% | 0.955 |
| Race/ethnicity | | | | | | |
| Non-Hispanic White | 44.6% | 45.3% | 46.5% | 43.6% | 44.2% | 0.646 |
| Non-Hispanic Black | 43.1% | 46.1% | 46.8% | 43.7% | 44.1% | 0.561 |
| Hispanic | 44.2% | 46.4% | 48.5% | 45.8% | 46.2% | 0.157 |
| Other[‖] | 42.4% | 43.5% | 45.6% | 40.3% | 44.6% | 0.395 |
| Primary source of payment | | | | | | |
| Private | 48.2% | 48.2% | 49.5% | 46.1% | 46.8% | 0.253 |
| Medicare | 32.6% | 35.1% | 37.0% | 35.3% | 36.4% | 0.003 |
| Medicaid | 43.0% | 46.8% | 46.7% | 44.7% | 45.3% | 0.067 |
| Other | 48.5% | 51.0% | 52.1% | 49.3% | 48.3% | 0.839 |

Note: α compares proportion (%) differences between 2006 and 2007 and 2014–2015, using a weight-corrected, Bonferroni-adjusted chi-squared statistic. *was based on ICD-9-CM diagnostic codes 140-239, 338.3X; [†]was based on ICD-9-CM codes 338.XX, 350.1X-350.2X, 354.4X, 355.71, 379.91, 388.7X, 719.4X, 724.1X-724.2X, 729.1X, 780.96, 786.5X, 789.XX; [‡]includes general/family practice, internal medicine, pediatrics, and obstetrics and gynecology; [§]includes psychiatry, general surgery, orthopedic surgery, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; [‖]includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups; and [¶]includes physician assistants (PAs) and nurse practitioners (NPs).

fentanyl to point-of-care screening tests, targeting illicit drug production into safer formulations that do not involve fentanyl, and revision of current legal penalties involving illicit opioid drug distribution (Frank and Pollack, 2017; Suzuki and El-Haddad, 2017; Xu et al., 2018).

In addition, enhancing public health measures to identify populations at increased risk and upscaling availability of treatment for opioid dependence is critical moving forward. Enrollment in both methadone and buprenorphine treatment programs has been shown to be protective against opioid overdose (Bruneau et al., 2018; Davoli et al., 2007; Esteban et al., 2003). A recent study estimates that in the United States, there are < 20 opioid therapy recipients per 100 injection drug users – this leaves much room for expansion and increased availability of opioid treatment programs (Larney et al., 2017). This strategy will target opioid use disorders stemming from both over-prescription and illicit opioid distribution.

The increase in non-opioid pain medication prescribing in both outpatient and emergency room settings is reassuring. Previous reports on pain medication, specifically in the ED, reported an increase in opioid prescribing and no change in non-opioid prescribing from 2001 to 2010 (Mazer-Amirshahi et al., 2014). Our results showed the

opposite, with an increase in non-opioid prescription. Our results suggest a response by ED providers to replace opioid treatments with non-opioid NSAIDs for patients presenting with pain disorder starting in 2010 (Dowell et al., 2016). Likewise, multiple studies in the primary care setting have shown the benefit of choosing non-opioid therapies for chronic pain – our results show that outpatient physicians are starting to use evidence-based guidelines for managing chronic pain (Renthal, 2016; Schneiderhan et al., 2017). Furthermore, WHO guidelines on pain prescribing have been updated to include greater specificity of pain type and recommend use of NSAIDs and non-opioids as well as non-pharmacologic treatments such as physiotherapy and occupational therapy before an initial prescription of a weak opioid (Vargas-Schaffer and Cogan, 2014). These strategies enable physicians to make clinical decisions that reduce long-term opioid dependence for their patients.

There are important limitations to this study. First, both NAMCS and NHAMCS limit the number of medications that are listed as prescribed during each visit. For patient visits where more than eight medications were prescribed, fentanyl or other opioid prescriptions, and especially NSAIDs (which are not consistently prescribed as they are available over the counter), may have not been captured, potentially underestimating pain medication prescribing. Second, NHAMCS only captures ED visits and does not include visits to hospital-based outpatient clinics, which limits the generalizability of our findings. Third, NAMCS and NHAMCS are representative of visits to physicians in the US, but they are likely to underestimate physician prescriptions as they excluded any prescription orders made by phone and do not capture physicians working in other settings (e.g., veterans' health affairs or long-term care facilities). Fourth, we did not explicitly test whether patterns of prescribing changed after the CDC guideline was issued or evaluate appropriateness of fentanyl prescribing; rather, our analysis is primarily descriptive, characterizing pain medication prescribing before and afterwards. Of note, change in clinical practice often occurs slowly and the 2013 release of the CDC guideline may not yet have been fully considered and implemented across health systems to observe its full effect in our study period of 2006–2015.

## 5. Conclusion

In summary, in this study of pain medication prescribing in a nationally-representative sample of outpatient and ED visits from 2006 to 2015, we found increased opioid pain medication prescribing in the outpatient setting, decreased opioid prescribing in the ED and an increased rate of fentanyl prescribing in the ED. These findings, consistent with state-level findings, suggest an illicit, non-prescription source of the fentanyl epidemic, rather than prescriptions by health care practitioners. To address current opioid crisis, both clinical and public health interventions are needed, such as targeted education outreach on evidence-based opioid prescribing and non-opioid alternatives, a multicomponent database system for prescription opioid monitoring and fostering guideline-recommended care, and increased nationwide access to opioid dependence treatment programs.

## Contributors

Study concept and design: all authors;
Data acquisition and statistical analyses: TGR;
Interpretation of data: all authors;
Drafting of manuscript: AV and TGR;
Critical revision of manuscript for important intellectual content: all authors;
Supervision: JSR.

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Please refer to the conflict of interest statement (see below).

## Role of the funder/sponsor

The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

## Previous presentation

None.

## Disclaimers

Publicly available data were obtained from the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). Analyses, interpretation, and conclusions are solely those of the author and do not necessarily reflect the views of the Division of Health Interview Statistics or NCHS of the CDC.

## Conflict of interest statement

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